Cyclic Peptide–Based Platform for Targeted Delivery to the Brain

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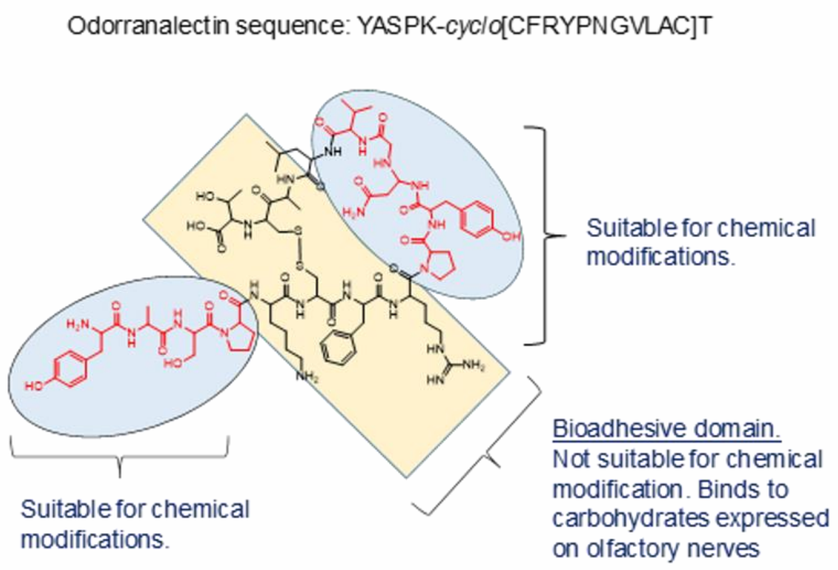
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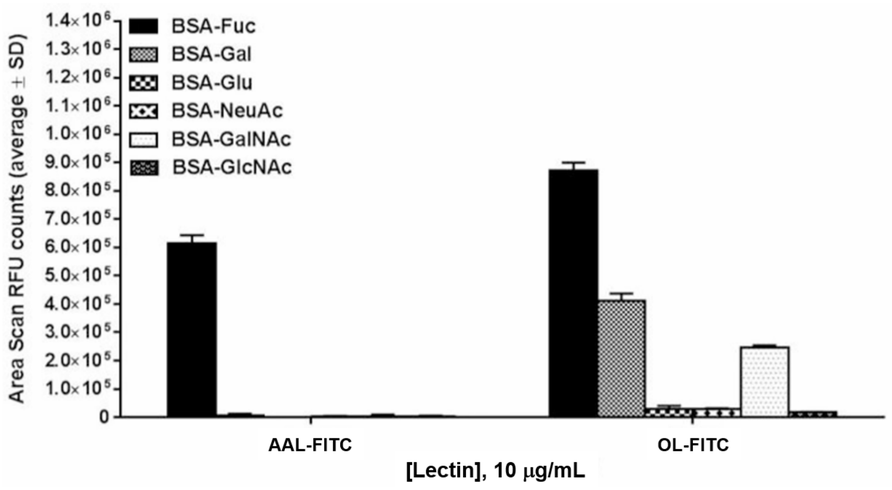
Introduction

Brain and central nervous system diseases are leading causes of disability worldwide, contributing substantially to hospitalization and long-term care. Peptides and small interfering RNA (siRNA) molecules offer significant therapeutic potential because of their ability to selectively target disease-associated proteins and genes. However, conventional delivery routes, such as oral and intravenous administration, are largely ineffective for transporting these molecules into the brain because of the restrictive nature of blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCB). Alternatively, intranasal (i.n.) delivery offers an attractive alternative that enables direct nose-to-brain delivery, bypassing these barriers while reducing systemic exposure and minimizing hepatic and renal clearance related toxicity.

Lectinomimic approach

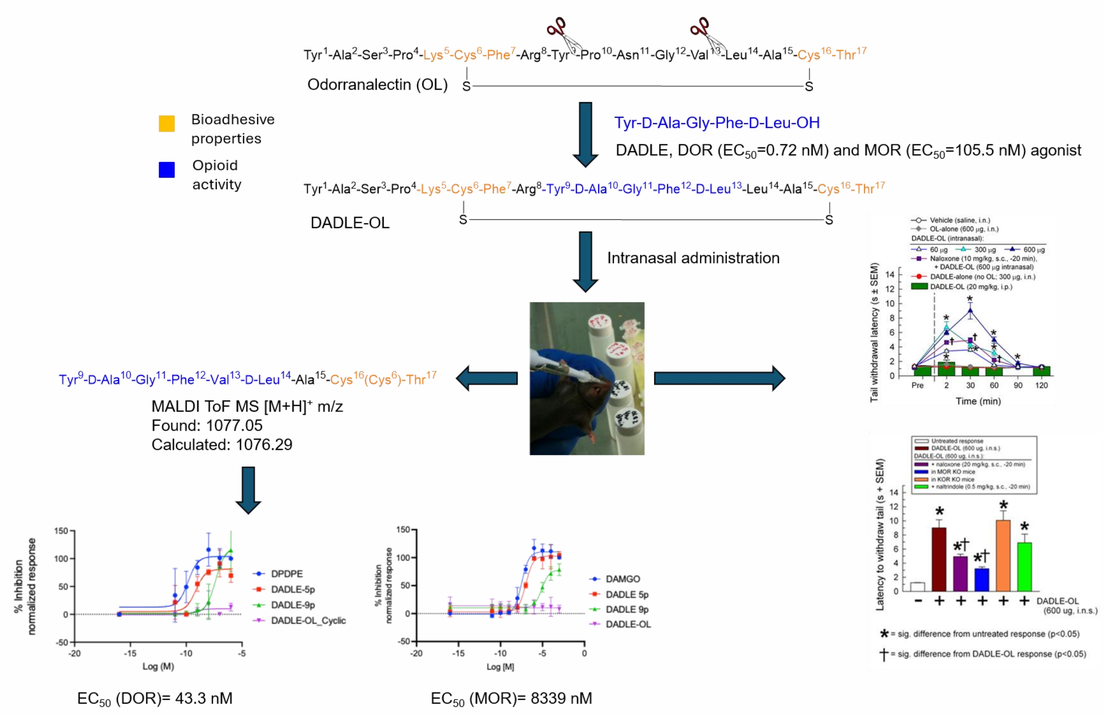
To enhance intranasal (i.n.) delivery of therapeutic peptides to the brain, we developed a novel strategy based on grafting a bioactive amino acid sequence onto the scaffold of the cyclic peptide odorranalectin (OL), which exhibits lectin-like properties. OL binds preferentially to L-fucose (Fuc) and, to a lesser extent, to D-galactose (Gal) and N-acetyl-D-galactosamine (GalNAc), carbohydrates that are widely distributed on the olfactory epithelium of the nasal mucosa. This binding profile suggests that OL may prolong residence time within the nasal cavity, thereby increasing mucosal retention and enhancing peptide absorption across the olfactory epithelium.





Binding of AAL-FITC and OL-FAM to BSA-monosaccharides.

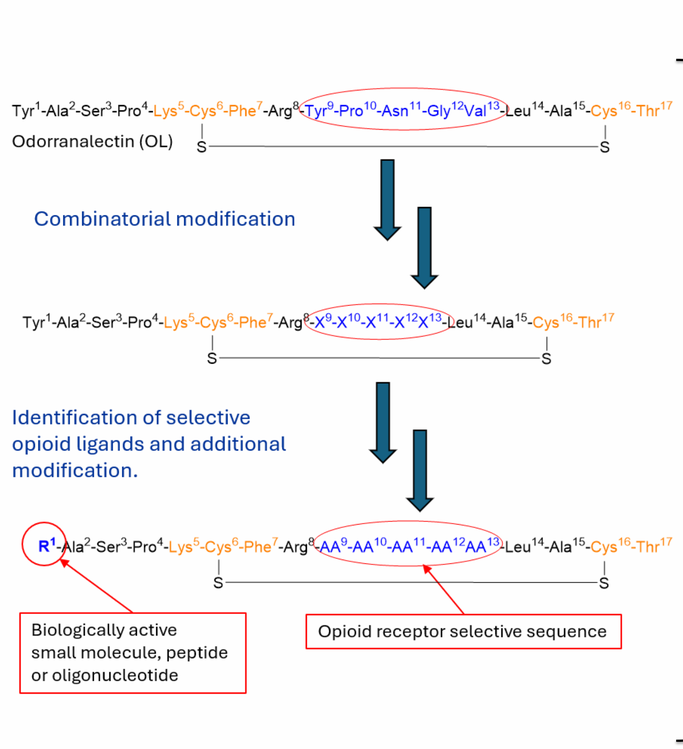
DADLE sequence grafting: proof of principle



Antinociceptive effects observed 2 min after i.n. administration. No effects observed after i.p. administration.

In vivo selectivity demonstrated by antinociception in wild-type, MOR-KO, KOR-KO, and in mice pre-dosed with naloxone and naltrindole.

OL-based KOR-selective ligand

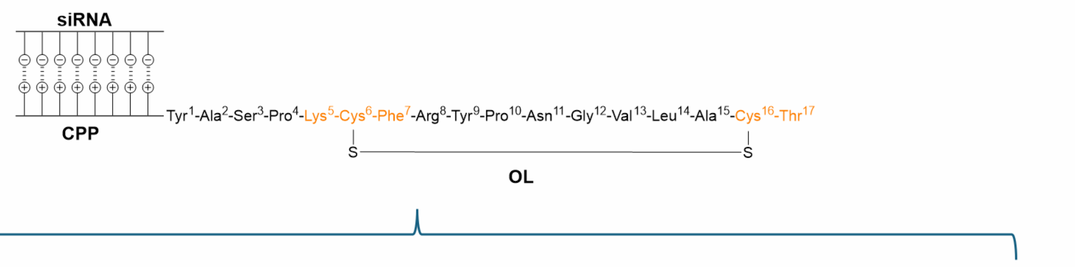


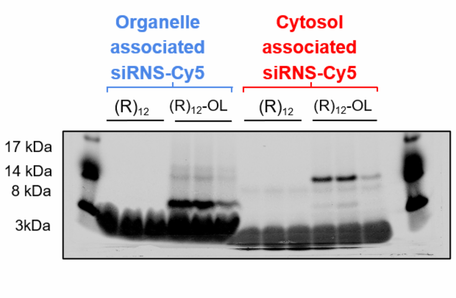
Improved *in vivo* selectivity.

More potent and longer lasting antiallodynic effects observed in the mouse chronic constriction injury (CCI) model of neuropathic pain compared to morphine.

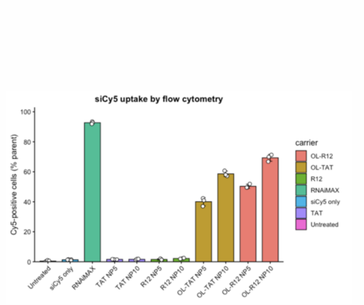
Effects on mice respiration.

OL-mediated cellular uptake of siRNA

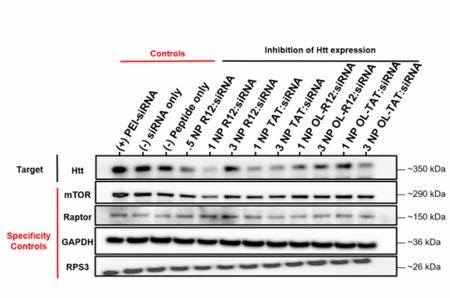




The size of the siRNA-Cy5 is conserved in the cytosolic fraction



siRNA-Cy5 uptake by flow cytometry (4h incubation)



Suppression of Huntingtin (htt) protein expression upon siRNA internalization in Q7 cells

Acknowledgment

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